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GYNECOLOGIC ONCOLOGY 13, 58–66 (1982)

Basement Membrane of the Uterine Cervix: Immunofluorescence Characteristics of the Collagen Component in Normal or Atypical Epithelium and Invasive Carcinoma

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Frozen sections of the uterine cervix were processed by an indirect immunofluorescence technique using specific antisera against type I, III, and IV collagens (raised in rabbits). A continuous basement membrane (BM) was selectively stained using antibodies against type IV collagens beneath both squamous and columnar epithelia. In the case of atypical epithelium, the appearance of BM beneath the epithelia remains unchanged. In contrast, with invasive carcinomas, a more or less continuous band of unequal thickness, whose reactivity in the presence of antibodies to type IV collagen remains weak or moderate, is observed around the lobules of neoplastic cells. Thus, the unimpaired character of the basement membrane cannot be considered as the major criterion, to distinguish carcinoma *in situ* from invasive carcinoma of the uterine cervix.

INTRODUCTION

The unimpaired character of the basement membrane (BM) is considered by many pathologists as the main criterion separating carcinoma *in situ* from invasive carcinoma of the uterine cervix, yet the BM is still sometimes difficult to visualize. Ultrastructural study (5) reveals that the lamina densa or BM, both homogeneous and microfibrillar, is separated from the cell by a lamina lucida and joined by anchoring fibrils to the surrounding connective tissue. This complex structure accounts for the difficulty in visualizing it under light microscopy. Histochemical reactions were at first employed, such as PAS (27), revealing the glycoprotein component or empirical silver staining reactions (where the substrate is not the BM proper but certain fibrils of the neighboring connective tissue).

In recent years, various authors: Rubio *et al.* [19–21], Pertschuk *et al.* [15, 16], Yamasaki *et al.* [26], have applied immunohistochemical procedures using antibodies from patients with bullous pemphigoid. In this paper, we propose to study the BM in its normal state, and the precancerous and cancerous states of

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the uterine cervix, utilizing
Spiro [22] and Kefalides *et*
type IV collagen associate
laminin [24], fibronectin [4

Materials

The tissue studied was d
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Immune Reagents

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the uterine cervix, utilizing specific antibodies to the different types of collagen. Spiro [22] and Kefalides *et al.* [12] have shown, in all the basement membranes, type IV collagen associated with various glycoprotein components, including laminin [24], fibronectin [4, 23], and one of a microfibrillar protein.

MATERIALS

Materials

The tissue studied was derived from 35 patients. There were 3 cases of normal epithelium, 19 of atypical epithelium (6 dysplasia and 13 carcinoma *in situ*), and 13 invasive squamous carcinomas (including 3 microinvasive carcinoma). Tissue was obtained at surgery by punch biopsy with colposcopic visualization, by cone biopsy, or at the time of definitive surgery. A small portion of each specimen was frozen and stored in liquid nitrogen and the remainder was submitted for routine histologic examination.

Immune Reagents

Specific antibodies are of two types: (a) sera from patients with histologically proven bullous pemphigoid (with high titers of antibodies against epithelial basement membrane) and sera from patients with malabsorption syndrome (I) containing antibodies to reticulin. All sera were kept frozen until the cervical tissues were examined; (b) antibodies to collagen types I, III, and IV.

Preparation of antigen (*8*). Collagen types I, III, and IV were prepared from fibrocytic human livers after limited pepsin digestion and fractional precipitation with sodium chloride according to the technique of Rhodes and Miller [18], modified for human liver by Chevalier *et al.* [6]; the purity of collagen fractions was controlled by sodium dodecyl sulfate–polyacrylamide gel electrophoresis. Bovine lens capsule type IV collagen was obtained using the technique of Dehm and Kefalides [7].

Preparation of specific antibodies. New Zealand white rabbits were injected subcutaneously every 2 weeks with 1 to 5 mg of pure native human collagen types I, III, and IV. The first injection was given with the antigen emulsified with Freund's complete adjuvant while the subsequent injections were made with antigen emulsified with incomplete adjuvant. The immunoglobin G (IgG) antibodies were separated from the crude immune sera by chromatography on a DEAE column (100 × 1 cm) equilibrated with 0.01*M* phosphate buffer, pH 8. Fab fragments were prepared by papain digestion of these IgG antibodies.

IgG antibodies or their Fab fragments directed specifically against type III and IV collagens were isolated by affinity chromatography of the IgG material or its Fab fragments on the corresponding collagen type bound to CnBr-activated Sepharose.

Antibodies cross-reacting with common determinants of the different collagen types were eliminated by absorbing the purified antibodies against one type of collagen with the other types bound to CnBr-activated Sepharose. The resulting material did not react with normal human serum using double diffusion or immunoelectrophoresis. Furthermore, its strict specificity for a single type of collagen was demonstrated by the following controls.

1. The direct hemagglutination of sheep red blood cells coated with one collagen type by the corresponding purified antibodies was inhibited by the addition of this collagen type but not by the other types.

2. The immunofluorescence of pure fibers of native collagen was obtained by an indirect reaction using the corresponding purified antibodies and a fluoresceinated goat anti-rabbit IgG. This reaction was extinguished by previous incubation of the antibodies with the corresponding collagen type but not by other collagen types.

METHODS

Immunofluorescence Staining Procedures

Immunolabeling of collagen type was realized by indirect immunofluorescence on 5-μm-thick unfixed frozen sections from the cervix, using the purified IgG antibodies (0.005 to 0.02 mg/ml) and a fluorescein isothiocyanate (FITC)—labeled sheep anti-rabbit IgG at 1/20 dilution. All readings were performed on a Leitz Orthoplan fluorescence microscope fitted with the Ploem incident illuminator and a CSI Philips Lamp. Immunofluorescent reactions were controlled by nonimmune rabbit serum or immune serum previously saturated with its specific antigen.

RESULTS

A. Normal Uterine Cervix (Figs. 1, 2)

Bovine antiserum to type IV collagen reveals a fine, continuous, fluorescent band beneath both the squamous epithelium and the columnar epithelium. When human antiserum to type IV collagen is used, the reactivity of the band is fainter. In both cases we can also find a fluorescent band beneath the capillary endo-

FIG. 1. Normal uterine cervix, × 250. Antiserum to type IV collagen. Presence of a fine, continuous fluorescent band beneath both the squamous epithelium (arrow) and the endothelium of the capillaries (double arrows).

FIG. 2. Normal uterine cervix
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B. Atypical Epithelium (Fi

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C. Invasive Squamous Ca

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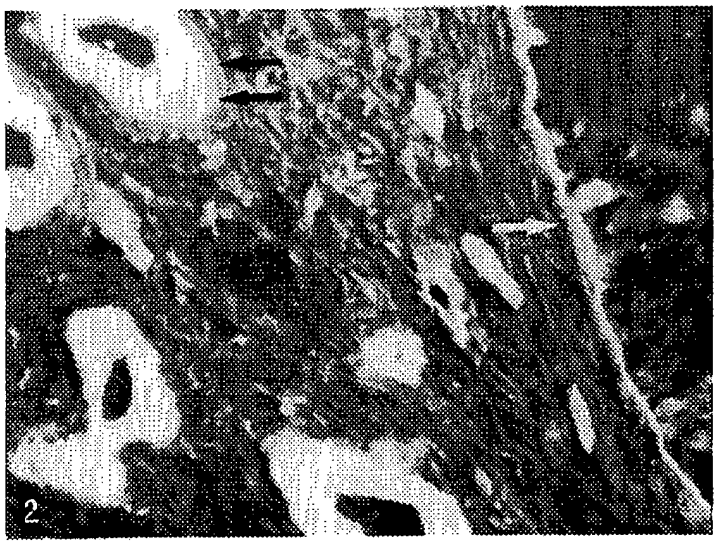

FIG. 2. Normal uterine cervix, × 250. Antiserum to type IV collagen. The columnar epithelium is underlined by a fine, continuous fluorescent band (arrow). There is also labeling of the sarcolemmic basement membranes of the arteriolar medias (double arrows).

thelium as well as at the level of the sarcolemmas of the arteriolar media, whereas the cervical stroma presents no reactivity.

When sections are treated with serum from patients with bullous pemphigoid, a faintly fluorescent linear deposit may be observed but there is some background fluorescence of the stroma.

With the other antibodies which tested (antibodies of coeliac disease, antiserum to collagen types III and I) no clearly defined or selective labeling of the basement membrane was observed, but only a diffuse fluorescence of the stroma.

B. Atypical Epithelium (Figs. 3, 4)

Antibodies to type IV collagen reveal a highly fluorescent band beneath the atypical surface epithelium and also at the level of the capillary basement membranes, accentuating a neoangiogenesis all the more important as the degree of epithelial atypia is pronounced. In the presence of antibodies of other specificity, the picture does not differ form that which we observed with regard to normal epithelium.

C. Invasive Squamous Carcinoma (Figs. 5, 6)

In the presence of antibodies to type IV collagen, there may be observed a fluorescent band underlining the atypical surface epithelium, generally in a fragmented and discontinuous manner. On the other hand, in depth, certain invasive lobules are also surrounded by a discontinuous immunoreactive basement membrane of uneven thickness, often of weaker reactivity, but variable from one point to another (10 cases out of 13). Abundant BM material of capillary walls

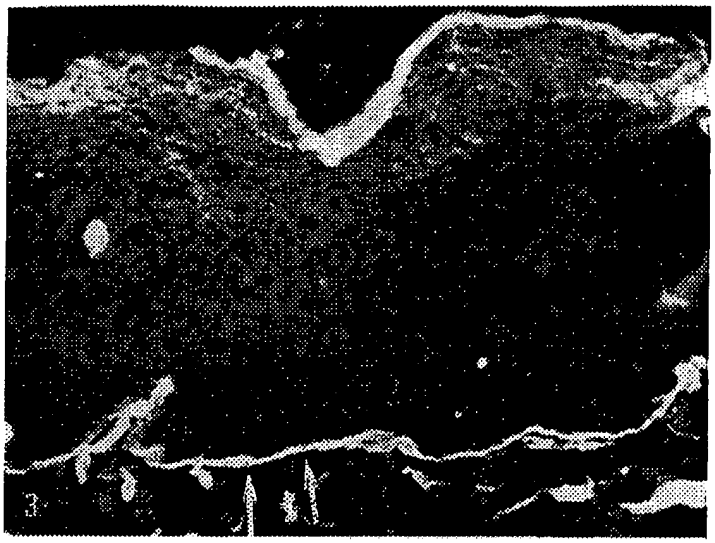

FIG. 3. Mild dysplasia of the uterine cervix, × 100. Antiserum to type IV collagen. The atypical epithelium rests on a fine, continuous fluorescent band (arrows). There is also nonspecific fluorescence of keratin at the periphery.

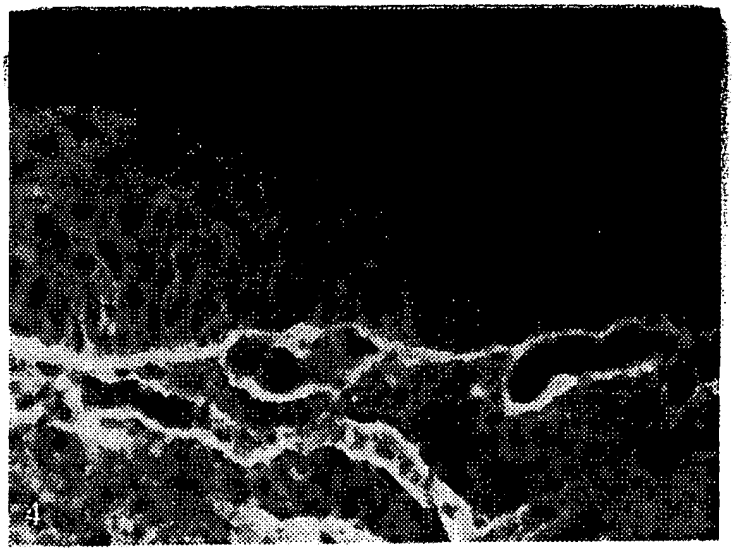

FIG. 4. Carcinoma *in situ*, × 250. Antiserum to type IV collagen. Beneath this lesion, there is a fine, continuous fluorescent band.

FIG. 5. Invasive squamous c
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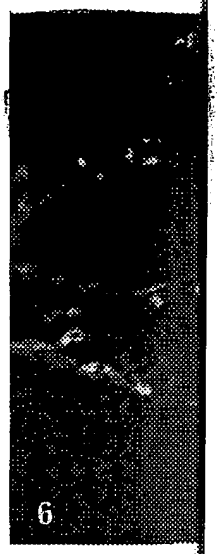

FIG. 6. Invasive squamous c
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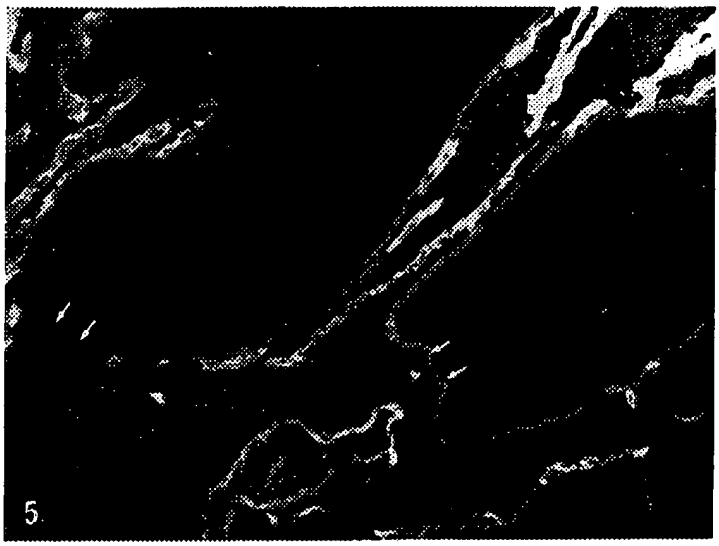

FIG. 5. Invasive squamous carcinoma of the uterine cervix, × 100. Antiserum to type IV collagen. The neoplastic lobules are outlined by a more or less fluorescent discontinuous band, of unequal thickness (arrows). The capillaries present fine, continuous basement membranes.

llagen. Beneath this lesion, there is

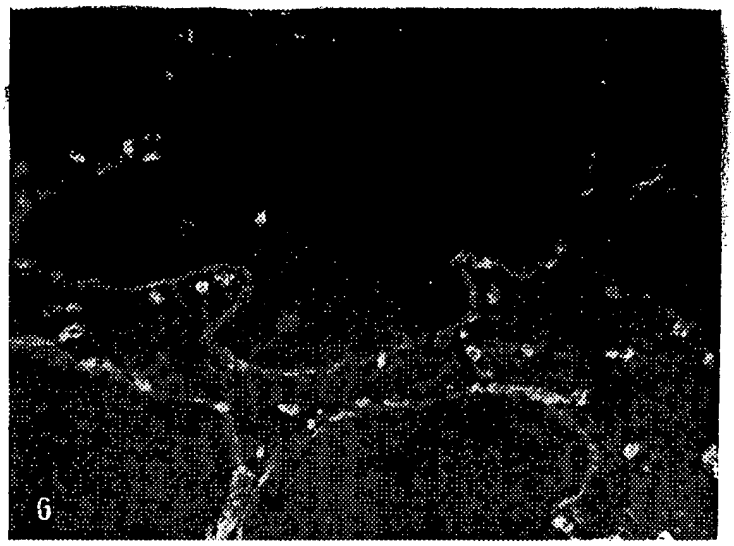

FIG. 6. Invasive squamous carcinoma of the uterine cervix, × 250. Antiserum to type IV collagen. Presence also of a more or less fluorescent discontinuous band of unequal thickness around the neoplastic cell lobules. Labeling of the capillary basement membranes reveals a marked neoangiogenesis.

was clearly shown by antibodies against type IV collagen. On the other hand, no noteworthy inter- or intracellular immunoreactive substance was seen. The antibodies against bullous pemphigoid also show the band with a much weaker reactivity.

Using antibodies against type III and I collagen or antireticulin antibodies a diffuse fluorescence of the chorion is observed and BM fluorescence is absent. The MacManus technique applied to adjacent sections confirms the existence of a PAS-positive staining band which appears discontinuous along the edge of the invasive lobules.

DISCUSSION

(I) Immunohistochemical Characterization of the BM of the Uterine Cervix

Beutner *et al.* [3] were the first to use circulating antibodies of patients with bullous pemphigoid to visualize the cutaneous BM by immunofluorescence. This technique was then applied to the uterine cervix by Pertschuk *et al.* [15, 16], Rubio *et al.* [21], and Yamasaki *et al.* [26] in the mouse. However, the antibodies give rise to a certain "background" and their specificity cannot be determined. Today specific antibodies against type IV collagen are used [9].

With the antibodies obtained by one of us [8], our work demonstrates the presence of this type of collagen in the BM of the uterine cervix, subepithelial or endothelial BM, and sarcolemnic BM of the arteriolar medias. This result confirms the immunochemical studies which have revealed the presence of $(\alpha\ 1\ IV)_3$ chains of MW $\neq$ 120,000 at the level of the basement membranes in adult tissues, trophoblasts, and some tumors.

The most convincing results have been observed with antiserum against type IV collagen obtained by using the antigen provided by the anterior bovine lens capsule. The presence of other collagen components may not be excluded as suggested by the high reactivity of the whole stroma with type I–III collagen antibodies.

(II) In the Case of Atypical Epithelium

No particular anomaly of the subepithelial BM was noted. Rubio *et al.* [19, 21] and Pertschuk *et al.* [16] using antibodies against bullous pemphigoid observed no anomalies of this membrane in cases of dysplasia or of *in situ* carcinoma.

(III) In Invasive Carcinomas

The presence of a more or less continuous band of unequal thickness surrounding some lobules has already been observed by the aforementioned authors who have used antibodies against bullous pemphigoid. The reactivity of this band in the presence of antibodies against type IV collagen remains weak or moderate. It may be related to the BM, as suggested by its PAS reactivity in light microscopy and electron microscopy.

(IV) The Significance of These Neobasement Membranes

Younes *et al.* [27] have suggested that it was a matter of condensation of the stromal fibers, but our immunohistochemical study does not account for this hypothesis.

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The work carried out by Kefalides *et al.* [12] suggests rather that the basement membranes are of epithelial or endothelial origin: the endothelial cells [11] and the myoepithelial cells [13] cultured *in vitro* produce the type IV collagen component. This property of synthesis and secretion also seems to be possessed by certain tumoral cells: Pierce [17], who cultivated two mammary carcinomas *in vitro* and a tumor of the granulosa, obtained the secretion of basement membranes by these tumors: the EMS sarcoma of the mouse [14, 24, 25] also has the same property and also secretes laminin.

Consequently, this secretion of the basement membrane by the tumoral cells appears to cast some doubt on its role as an antitumoral barrier, all the more so as the basement membranes act as a support in the migration of certain embryonic cells [10].

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